Cancer-specific ultraconserved long noncoding RNA 8 as a novel biomarker for early bladder cancer detection

Daniela Terracciano¹, Matteo Ferro², Angelo Ciaramella³, Giovanna L. Liguori⁴, Valerio Costa⁴, Ferdinando Febbraio⁵, Amelia Cimmino⁴

¹Department of Translational Medical Sciences, University of Naples "Federico II," Naples, Italy
²Division of Urology, European Institute of Oncology, Milan, Italy
³Department of Science and Technology, University of Naples Parthenope, Naples, Italy
⁴Institute of Genetics and Biophysics “A. Buzzati Traverso”, National Research Council (CNR), Naples, Italy
⁵Institute of Biochemistry and Cell Biology, National Research Council (CNR), Naples, Italy

Bladder cancer (BICa) is among the most common malignant tumors of the urological system, ranking ninth in worldwide cancer incidence and fourth in men in the USA and is one of the most expensive malignancies in men, in terms of treatment costs worldwide [1]. The most common form is non-muscle-invasive bladder cancer (NMIBC), which accounts for 75% of newly diagnosed BICa, while the muscle-invasive form (MIBC) accounts for the remaining part [2,3]. Ultraconserved regions (UCRs) are approximately 480 sequences in the human genome showing a 100% identity with orthologous sequences in rats and mice, point out that they went through a very strong negative selection for 300–400 million years; these regions are called “ultraconserved” [4]. In literature, T-UCRs molecular details in terms of RNA size and sequence have been described, and in some cases (only 19 T-UCRs, 3.95%), molecular mechanisms have also been explored [5]. Unlike mRNAs, which must localized to the cytoplasm for protein synthesis, IncRNAs exhibit diverse subcellular distribution patterns, ranging from predominant nuclear foci to almost exclusively cytoplasmic localization, and exert distinct regulatory effects at their particular site of action [9,10]. Thus, the subcellular localization of IncRNAs plays an important role for their biological function. In our work, we analyzed the effects of the localization in different cellular compartments of a IncRNA containing the transcribed ultraconserved region 8 (uc.8+) on samples from pts affected by BICa. In this study, we further evaluated by in situ hybridization the expression of the newly identified uc.8+ in a panel of 73 human BICa specimens. We adopt DeepLncRNA (Deep Learning of Nuclear Classification of long non-coding RNAs) [6], a novel Deep Learning model learned for predicting IncRNA subcellular localization directly from IncRNA nucleotide sequences. We found that ultra-conserved-transcript-8+ (uc.8+) levels correlate both with grading and staging of bladder cancer. Subcellular-localization analyses indicated the simultaneous presence of uc.8+ in the cytoplasm and nuclei of cells in Low-Grade group samples, while, a cytoplasmic localization was observed in samples from High-Grade group, supporting the cyto-nuclear translocation of uc.8+ with a less tumor malignancy. Also, measurements of uc.8+ expression and subcellular localization in tumor-surrounding stroma, revealed an overall reduction of uc.8+ intensity, with a marked down-regulation compared to the paired adjacent tumor region. Deep machine-learning approaches identified sequences associated with uc.8+ localization in nucleus and/or cytosol, allowing to identify RNA binding proteins, recognizing these sequences, involved in mRNA cytosol-translocation. Our model suggested that uc.8+ localization could be a prognostic biomarker. Moreover, on the basis of our preliminary results about the detection of uc.8+ in the urine, we will provide evidence about the use of uc.8+, as urinary marker for early-diagnosis and recurrence of bladder cancer alone or in combination whit other candidate biomarkers.
References:


Keywords: Bladder cancer; prognostic biomarker; ultraconserved region; Transcribed-ultraconserved region; long noncoding RNA; ultraconserved transcript 8+: uc.8+;

Contacts: amelia.cimmino@igb.cnr.it

Website(s): http://www.igb.cnr.it/staff/people/cimmino

Abbreviations: UCR: ultraconserved region; T-UCR: Transcribed-ultraconserved region; lncRNA: long noncoding RNA; Bladder cancer: BlCa.